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RESEARCH REPORT

Expanding Our Understanding of Lower Urinary Tract Symptoms and Incontinence in Adults with Pompe Disease

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Abstract *Objective:* To study the prevalence of lower urinary tract symptoms (LUTS) and incontinence in late-onset Pompe disease (LOPD)

Methods: Adult LOPD patients seen at the Duke Pompe Clinic were prospectively recruited and asked to complete validated questionnaires on LUTS and incontinence as part of an IRB-approved study. Patient demographics as well as previous urologic history were reviewed.

Results: 35 patients with LOPD were included in the study (17 males and 18 females). The median age was 51.8 (range 18–72 years of age). Of these patients, 27/35 were receiving enzyme replacement therapy (ERT) with median duration of 54 months (range 5–88 months). In the male patients, 9/17 (53%) described their stream as dribbling, weak, or intermittent, and 9/17 (53%) complained of post-void dribbling. In addition 38% of the men were unable to stop their urination midstream. In the female patients, the most common complaint was urinary incontinence, reported in 14/18 (78%). In addition, 7/18 (39%) complained of post-void dribbling, and 47% were unable to stop their urination midstream. Bowel incontinence was reported in 45% of patients. There was a significant association between urinary symptoms and lower extremity function scores and duration of ERT ($p = 0.005$ and $p = 0.04$, respectively)

Conclusions: This is the first study in a large cohort of LOPD patients that demonstrates LUTS and incontinence occur at a high rate. This study emphasizes the spectrum of LOPD is beyond isolated gross motor and pulmonary involvement and has a significant effect on the lower urinary tract.

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Introduction

Pompe disease (glycogen storage disease type II) is an autosomal recessive disorder caused by mutations in the gene that encodes alpha-1,4-glucosidase (GAA). The incidence of Pompe disease across the disease spectrum has been reported to be 1 in 40,000 (Martiniuk et al. 1998). Late-onset Pompe disease (LOPD) can present anytime from after the first year of life to as late as the sixth decade, with considerable phenotypic heterogeneity. The most common complaints are progressive weakness in a limb-girdle distribution and up to 30% may present with respiratory issues (Hagemans et al. 2005).

Glycogen accumulation within the skeletal muscles as well as the organs containing the smooth muscle (the bladder, intestine, and esophagus) has been demonstrated in autopsy reports (Hobson-Webb et al. 2012). These findings support the various clinical symptoms of the disease seen in this population such as urinary and fecal incontinence, dysphagia, gastroesophageal reflux, and gastrointestinal dysmotility. Urinary incontinence has been previously

described in other neuromuscular and neurological disorders but has not yet been studied within the LOPD population (van der Walt et al. 1987; Kobayashi et al. 2010; Fidzianska et al. 2011). There are case reports that look at incontinence, mainly fecal incontinence, with relationship to enzyme replacement therapy (ERT) (Remiche et al. 2012).

The goal of this study was to systematically collect validated patient questionnaires that evaluated lower urinary tract symptoms (LUTS), urinary and fecal incontinence, as well as patient demographics and disease severity to better understand the prevalence of LUTS and incontinence within this population. We hypothesized that the glycogen accumulation in this disease process has a deleterious effect on urinary function in adults with LOPD.

Methods

Patient Population

Adult patients with LOPD seen as a part of the Duke Pompe Clinic at Duke University Medical Center were asked to fill out validated questionnaires on LUTS and incontinence. This study was IRB approved, and all patients signed consent prior to data collection.

Questionnaire Details

The following questionnaires were given to each patient according to gender: (1) Male/Female Incontinence Impact Questionnaire, (2) Male/Female Urogenital Distress Inventory, and (3) AUASS (American Urologic Association Symptom Score and Quality of Life). These are validated questionnaires used in the urology and urogynecology literature to evaluate lower urinary tract symptoms and urinary incontinence as well as bother scores. These questionnaires focus on frequency and description of urination, stress and urgency incontinence, and other associated symptoms. They also address impact of urinary symptoms on activities and quality of life. There are questions that ask about previous urologic and incontinence history as well as relevant medications used for LUTS and incontinence. To address other etiologies of bladder complaints, questions were added that assessed urinary tract infections, number of infections, and presence of hematuria. In addition to bladder function, these questionnaires obtain data on bowel function, including the presence of constipation or diarrhea, pain with bowel movements, and problems with losing gas, loss of loose or solid stool, and number of episodes per week.

Medical records of all patients were reviewed for patient demographics, including age and gender as well as urologic history. With regard to Pompe disease status, we reviewed the age at onset of LOPD, the disease duration, treatment with ERT or not, and ERT duration. In order to analyze functional status with respect to urinary continence, the 6-minute walk test (6MWT) results were reviewed for each patient as well as the use of ambulatory assistive devices and upper and lower extremity functional scores rated by a licensed physical therapist (LC) (Personius et al. 1994; Laboratories 2002). We determined pulmonary status of patients by their current use of BIPAP.

Statistical Analysis

We used descriptive statistics to define the study population. Bivariate associations between potentially important clinical factors and the presence of urinary symptoms were evaluated by using Mann–Whitney test for continuous variables and Fisher's exact test for binary variables, and statistical significance was set at $p < 0.05$ on two-tailed analysis (GraphPad Prism 6®).

Results

A total of 35 adult patients seen at the Duke Pompe Clinic completed the validated questionnaires in the period April 2012–July 2013. Only three patients with LOPD seen at our clinic did not consent to the study and were not included. Demographics and disease characteristics by gender are presented in Table 1. Of the 35 patients, 17 were male and 18 were female. For the overall cohort, the median age was 51.8 years of age (range 18–72 years old), the median duration of disease was 69.6 months (range 1–244 months), 77% were on ERT, and median duration of ERT was 54 months (range 5–88 months).

In our adult LOPD cohort, 23/35 (65.7%) reported at least one lower urinary tract symptom on the questionnaires. The most frequently mentioned symptoms were urinary incontinence, weak stream, post-void dribbling, and inability to stop urinary stream. The symptoms varied by gender. These results of the questionnaires by gender are shown in Table 2. Males were more likely to report weak stream, post-void dribbling, and inability to stop stream. Females were more likely to report urinary incontinence and fecal incontinence. For the overall cohort, 14/35 (40%) reported weak stream, 16/35 (45.7%) reported post-void dribbling, 12/28 (42.9%) reported inability to stop urinary stream, 19/35 (54%) reported urinary incontinence, 8/35 (22.9%) reported incomplete emptying, and 14/31 (45.2%) reported fecal incontinence. There were no patients in our

Table 1 Demographic characteristics of cohort by gender

Characteristics	Male ($N = 17$)	Female ($N = 18$)
Age in years, median (IQR)	50 (20.8)	53.3 (14.2)
Duration of disease, months median (IQR)	54 (68.4)	82.8 (172.8)
ERT, *N* (%)	16 (94)	11 (61)
Duration of ERT, months median (IQR)	39.6 (44.4)	61.2 (48)
Ambulatory assistance, *N* (%)	6 (35)	12 (67)
Upper extremity functional score, *N* (%)		
1	12 (71)	13 (72)
2	2 (12)	3 (17)
3	2 (12)	1 (5.5)
Missing	1	1
Lower extremity functional score, N (%)		
1	9 (53)	4 (22)
2	5 (29)	4 (22)
3	0 (0)	4 (22)
6	2 (12)	5 (28)
Missing	1	1
6 MWT in meters median (IQR)	410.8 (111.4)	320.2 (175.2)
Use of Bipap, *N* (%)	11 (64.7)	5 (27.8)

Table 2 Results from questionnaire by gender

Questionnaire results	Male, *N* (%)	Female, *N* (%)
Weak, intermittent, dribbling urinary stream	9/17 (53)	5/18 (28)
Post-void dribbling	9/17 (53)	7/18 (39)
Inability to stop stream	5/13 (38)	7/15 (47)
Urinary incontinence	5/17 (29)	14/18 (78)
Stress	0 (0)	4 (28.6)
Urge	5 (100)	6 (42.8)
Both	0 (0)	4 (28.6)
Fecal incontinence (loose stool at least 2 times/week)	3/16 (19)	11/15 (73)
QOL: frustration, interference with daily activities, overall bother	7/17 (41)	8/18 (44)

cohort that reported hematuria, and only one patient reported pain with urination. Bladder infections were reported in 5/35 (14.2%) with an average of 2.4 infections/year. Only one patient was on an anticholinergic medication for lower urinary tract symptoms, and no patients reported any surgery related to urinary symptoms. While obstetric history was not obtained, no female patients reported vaginal symptoms. When asked about quality-of-life parameters, 15/35 (42.9%) reported frustration, interference with activities, or overall bother from their urinary symptoms.

On bivariate analysis, factors significantly associated with lower urinary tract symptoms included the following: duration of ERT ($p = 0.04$), lower extremity functional scores ($p = 0.005$), and the 6MWT ($p = 0.003$). Age, gender, duration of disease, treatment with ERT vs. not on ERT, the use of ambulatory assistance device, and the use of BIPAP were not significantly associated with urinary symptoms on bivariate analysis. The odds ratio of having bowel incontinence in patients with bladder incontinence was 4.1 (95% CI 0.8–20.3, $p = 0.07$). See Table 3.

Discussion

In our cohort, LUTS and urinary and fecal incontinence were seen in a large percentage of adult LOPD patients. Age, gender, duration of disease, treatment with ERT, need

Table 3 Bivariate association of clinical characteristics and urinary symptoms

Characteristics	No urinary symptoms ($N = 12$)	Urinary symptoms ($N = 23$)	p-value
Age			
<50	8 (66.7)	7 (30.4)	0.07[a]
≥50	4 (33.3)	16 (69.6)	
Gender, *N* (%)			
Male	8 (66.7)	9 (39.1)	0.16[a]
Female	4 (33.3)	14 (60.9)	
Duration of disease in months, median (IQR)	37.5 (97.5)	87 (111)	0.38[b]
Use of ERT, N (%)	11 (91.7)	16 (69.6)	0.22[a]
Duration of ERT in months, median (IQR)	33 (31)	59 (42)	0.04[b]
Use of ambulatory assistance, *N* (%)	3 (25)	15 (65.2)	0.07[a]
LE functional scores ≥3	0 (0)	11 (47.8)	0.005[a]
6 MWT in meters, median (IQR)	415.8 (124.4)	335 (188.5)	0.003[b]
Use of BIPAP, *N* (%)	5 (41.7)	11 (47.8)	1[a]

[a] Fisher's exact test, two tailed
[b] Mann–Whitney test, two tailed

for ambulatory assistance, and the use of BIPAP were not significantly associated with the presence of these symptoms. However, duration of ERT treatment, lower extremity functional scores, and the 6MWT were significantly associated with symptoms, and patients with bladder incontinence had higher odds of having bowel incontinence.

To date, there has only been one other study looking at urinary incontinence in this patient population. Remiche et al. described five patients, four of which had fecal incontinence and one that had both urinary and fecal incontinence. In their study, they concluded that patients with LOPD had a higher prevalence of incontinence and that there may be improvement with ERT (Remiche et al. 2012). Our study findings expand the knowledge of the prevalence of urinary symptoms as our data indicates a high prevalence of symptoms across all ages and stages of disease.

The prevalence of urinary incontinence in our cohort was much higher and occurred at a younger age than in the general population. In healthy men, urinary incontinence has been reported in 17% of the population with the prevalence being lowest in men under 69 years of age (11%) and highest in men older than 85 (31%) (Anger et al. 2006). In our study, all five of the men (29.4%) that reported urinary incontinence were 62 years old or younger. Other studies show prevalence of female incontinence to range from 15 to 50% within the community (Minassian et al. 2003; Wallner et al. 2009; Cameron et al. 2013; Matthews et al. 2013). The incontinence rate in our population was much higher at 78%. Lower urinary tract symptoms (LUTS) are also seen at much lower rates within the community compared to our LOPD population. A large population-based study reported the 5-year incidence of LUTS to be 11.4% (8.5% in men and 13.9% in women) and a prevalence of 20% (Maserejian et al. 2013a, b). In our cohort we saw a prevalence of 52.9% in the men and 77.8% in women. Fecal incontinence has also been shown within the population to have a low prevalence of 4–25%(Halland et al. 2013; Matthews et al. 2013). The prevalence of fecal incontinence in the adult LOPD cohort was much higher at 45.2% overall and 73% when we look just at the females.

Our results indicate that this problem is significantly underdiagnosed and possibly undertreated in this population. The difference in urinary symptoms between genders can be explained by the anatomy of the urinary tract. More men have post-void dribbling and weak stream secondary to the length of the urethra and the involvement of the bulbospongiosus muscle in voiding. There is also the issue of the prostatic enlargement that may lead to urinary symptoms. Women, in general, have higher rates of urinary incontinence and have both stress and urge incontinence as they age, related to the pelvic floor inadequacy. In our group we looked at age and prevalence of urinary symptoms, and this did not differ between those older than 50 years of age and younger than 50.

While this study cannot answer the question of pathophysiology of LUTS and incontinence, we hypothesize that these symptoms are most likely related to the underlying disease process of glycogen deposition in the skeletal and smooth muscles. Autopsy reports have shown glycogen deposition within the smooth muscle of bladder

(Hobson-Webb et al. 2012). This is also demonstrated in the animal model of infantile Pompe disease (Bijvoet et al. 1998). An alternative etiology could be the effect on the autonomic nervous system and peripheral nerves that innervate the lower urinary tract. Pompe disease does affect the peripheral nerves, and glycogen may deposit in the axons, although there is conflicting data (van der Walt et al. 1987; Kobayashi et al. 2010; Fidzianska et al. 2011). The symptomatology may direct us to study the detrusor smooth muscle of the bladder, and skeletal muscles of the internal and external sphincter and the pelvic floor in LOPD, all of which play key roles in voiding and continence. The first step is identifying patients who have urinary symptoms and referring them to the appropriate specialist, urology or urogynecology, and sometimes gastroenterology for fecal incontinence. There are treatment options for the myriad of urinary symptoms that are seen in our LOPD patient cohort.

In addition to describing LUTS and incontinence in this population, we were also able to look at the impact of these symptoms on quality of life. Several studies have looked at QOL in LOPD and have found that it is greatly affected by the disease state (Hagemans et al. 2004, 2005; Wokke et al. 2008). There is also literature that shows a decrease in QOL secondary to urinary symptoms within other populations (Naughton et al. 2004; Basra and Kelleher 2007; Howard and Steggall 2010). This has not been studied before in LOPD, but in our cohort, greater than 40% of patients reported frustration, interference, or bother secondary to urinary symptoms. This is an important measure that can be monitored as patients are treated for LOPD and possibly treated for urinary symptoms. As ERT has been successful in improving survival in this patient population, QOL should be an additional primary end point for treatment. Since the advent of ERT, natural history is emerging and new aspects of the disease are being recognized, including other smooth muscle and skeletal muscle involvement and peripheral nerve involvement.

These data must be interpreted within the context of the study design. This is a small patient cohort; however, it is the largest study looking at LUTS and incontinence in the LOPD population. We believe that this data is generalizable to this specific patient population. Because this is a cross-sectional study, we are unable to make any conclusions about the initiation and role of ERT and relation to urinary symptoms and incontinence. Further study needs to be done to collect longitudinal data to study this relationship. More in-depth evaluation of urinary symptoms by urodynamic and urologic/urogynecologic evaluation may elucidate causes of urinary symptoms and incontinence and may be important in developing treatment options.

Conclusion

This study emphasizes that the spectrum of LOPD is beyond isolated gross motor involvement with pulmonary involvement. The prevalence of LUTS and incontinence are significantly higher in patients with LOPD. Our data indicates that these problems may be significantly under-diagnosed and therefore undertreated. The recognition of these issues in adults with LOPD should be emphasized as treatments for these problems can significantly improve quality of life. Further emphasis on the study of the etiology of LUTS and incontinence in this population is needed in order to direct future treatment.

Synopsis

This study highlights an underdiagnosed problem in a large cohort of LOPD patients and describes the prevalence of urinary symptoms and urinary and fecal incontinence.

Compliance with Ethics Guidelines

Funding source: No external funding was secured for this study.

Conflict of Interest

- Dr. McNamara reports no disclosures.
- Stephanie Austin reports no disclosures.
- Lauren Case has received honoraria from Genzyme Corporation of Sanofi; has participated in research supported by Genzyme Corporation of Sanofi, PTC Therapeutics, the Leal Foundation, Families of SMA, Enobia Pharma Inc./Alexion, the Robertson Foundation, and GlaxoSmithKline; has been awarded grant support from the National Skeletal Muscle Research Center; and is a member of the Pompe Registry Board of Advisors for Genzyme Corporation of Sanofi.
- Dr. Wiener has served as a consultant to Eli Lilly and Company.
- Dr. Peterson has no disclosures.
- Dr. Kishnani has received research/grant support and honoraria from Genzyme Corporation and is a member of the Pompe and Gaucher Disease Registry Advisory Board for Genzyme Corporation.

All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Authorship: All authors have given final approval of the version to be published.

Erin R. McNamara – Dr. McNamara contributed to collection, analysis, or interpretation of the data as well as drafting the manuscript. This author completed all statistical analysis.

Stephanie Austin – Contributed to collection and interpretation of the data as well as revising the manuscript.

Laura Case – Contributed to interpretation of the data as well as revising the manuscript.

John S. Wiener – Contributed to design and conceptualization of the study and interpretation of the data as well as revising the manuscript.

Andrew C. Peterson – Contributed to design and conceptualization of the study and interpretation of the data as well as revising the manuscript.

Priya S. Kishnani – Contributed to design and conceptualization of the study and interpretation of the data as well as revising the manuscript.

References

Anger JT, Saigal CS, Stothers L, Thom DH, Rodriguez LV, Litwin MS, Urologic P, Diseases of America (2006) The prevalence of urinary incontinence among community dwelling men: results from the national health and nutrition examination survey. J Urol 176(5):2103–2108, discussion 2108

Basra R, Kelleher C (2007) Disease burden of overactive bladder: quality-of-life data assessed using ICI-recommended instruments. Pharmacoeconomics 25(2):129–142

Bijvoet AG, van de Kamp EH, Kroos MA, Ding JH, Yang BZ, Visser P, Bakker CE, Verbeet MP, Oostra BA, Reuser AJ, van der Ploeg AT (1998) Generalized glycogen storage and cardiomegaly in a knockout mouse model of Pompe disease. Hum Mol Genet 7(1):53–62

Cameron AP, Heidelbaugh JJ, Jimbo M (2013) Diagnosis and office-based treatment of urinary incontinence in adults. Part one: diagnosis and testing. Ther Adv Urol 5(4):181–187

Fidzianska A, Lugowska A, Tylki-Szymanska A (2011) Late form of Pompe disease with glycogen storage in peripheral nerves axons. J Neurol Sci 301(1–2):59–62

Hagemans ML, Janssens AC, Winkel LP, Sieradzan KA, Reuser AJ, Van Doorn PA, Van der Ploeg AT (2004) Late-onset Pompe disease primarily affects quality of life in physical health domains. Neurology 63(9):1688–1692

Hagemans ML, Winkel LP, Hop WC, Reuser AJ, Van Doorn PA, Van der Ploeg AT (2005) Disease severity in children and adults with Pompe disease related to age and disease duration. Neurology 64 (12):2139–2141

Halland M, Koloski NA, Jones M, Byles J, Chiarelli P, Forder P, Talley NJ (2013) Prevalence correlates and impact of fecal incontinence among older women. Dis Colon Rectum 56 (9):1080–1086

Hobson-Webb LD, Proia AD, Thurberg BL, Banugaria S, Prater SN, Kishnani PS (2012) Autopsy findings in late-onset Pompe disease: a case report and systematic review of the literature. Mol Genet Metab 106(4):462–469

Howard F, Steggall M (2010) Urinary incontinence in women: quality of life and help-seeking. Br J Nurs 19(12):742, 744, 746, 748–749

Kobayashi H, Shimada Y, Ikegami M, Kawai T, Sakurai K, Urashima T, Ijima M, Fujiwara M, Kaneshiro E, Ohashi T, Eto Y, Ishigaki K, Osawa M, Kyosen SO, Ida H (2010) Prognostic factors for the late onset Pompe disease with enzyme replacement therapy: from our experience of 4 cases including an autopsy case. Mol Genet Metab 100(1):14–19

Laboratories A. T. S. C. o. P. S. f. C. P. F (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166(1):111–117

Martiniuk F, Chen A, Mack A, Arvanitopoulos E, Chen Y, Rom WN, Codd WJ, Hanna B, Alcabes P, Raben N, Plotz P (1998) Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. Am J Med Genet 79(1):69–72

Maserejian NN, Chen S, Chiu GR, Araujo AN, Kupelian V, Hall SA, McKinlay JB (2013a) Treatment status and progression or regression of lower urinary tract symptoms among adults in a general population sample. J Urol 191(1):107–113

Maserejian NN, Chen S, Chiu GR, Wager CG, Kupelian V, Araujo AB, McKinlay JB (2013b) Incidence of lower urinary tract symptoms in a population-based study of men and women. Urology 82(3):560–564

Matthews CA, Whitehead WE, Townsend MK, Grodstein F (2013) Risk factors for urinary, fecal, or dual incontinence in the nurses' health study. Obstet Gynecol 122(3):539–545

Minassian VA, Drutz HP, Al-Badr A (2003) Urinary incontinence as a worldwide problem. Int J Gynaecol Obstet 82(3):327–338

Naughton MJ, Donovan J, Badia X, Corcos J, Gotoh M, Kelleher C, Lukacs B, Shaw C (2004) Symptom severity and QOL scales for urinary incontinence. Gastroenterology 126(1 Suppl 1): S114–S123

Personius KE, Pandya S, King WM, Tawil R, McDermott MP (1994) Facioscapulohumeral dystrophy natural history study: standardization of testing procedures and reliability of measurements. The FSH DY Group. Phys Ther 74(3):253–263

Remiche G, Herbaut AG, Ronchi D, Lamperti C, Magri F, Moggio M, Bresolin N, Comi GP (2012) Incontinence in late-onset Pompe disease: an underdiagnosed treatable condition. Eur Neurol 68 (2):75–78

van der Walt JD, Swash M, Leake J, Cox EL (1987) The pattern of involvement of adult-onset acid maltase deficiency at autopsy. Muscle Nerve 10(3):272–281

Wallner LP, Porten S, Meenan RT, O'Keefe Rosetti MC, Calhoun EA, Sarma AV, Clemens JQ (2009) Prevalence and severity of undiagnosed urinary incontinence in women. Am J Med 122 (11):1037–1042

Wokke JH, Escolar DM, Pestronk A, Jaffe KM, Carter GT, van den Berg LH, Florence JM, Mayhew J, Skrinar A, Corzo D, Laforet P (2008) Clinical features of late-onset Pompe disease: a prospective cohort study. Muscle Nerve 38(4):1236–1245